EDITORIAL

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Obesity Paradox in the Course of Cerebrovascular Diseases

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article; **G** – other

Abstract

Obesity remains an important risk factor of cardiovascular and cerebrovascular diseases. However, it has been observed that increased body fat and body mass index predicted longer survival after the occurrence of a cardiovascular event. This observation has been named the obesity paradox. Initially, the term obesity paradox referred to the observation of the better outcome of cardiovascular diseases, such as heart failure and coronary heart disease, in obese patients as compared to underweight and normal-weight patients. Recently, similar, although fewer, observations confirm the occurrence of the obesity paradox in patients with acute cerebrovascular diseases. The underlying reasons for the protective effects of excessive body fat tissue against the consequences of acute cardiovascular and cerebrovascular diseases are poorly understood. The effect of preconditioning may be associated with the obesity paradox. The issue of the correlation between obesity and better survival of patients with cardiovascular and cerebrovascular diseases still remains largely unexplored. Debates for and against the obesity paradox continue (**Adv Clin Exp Med 2015, 24, 3, 379–383**).

Key words: obesity, obesity paradox, cerebrovascular diseases, cardiovascular diseases, preconditioning.

Epidemiological and Clinical Studies

The constantly increasing incidence of obesity constitutes a great public health problem. Obesity – leading to increased total blood volume, cardiac output, and cardiac workload – may be associated with increased arterial blood pressure, dyslipidemia, glucose abnormalities or insulin resistance, prothrombotic/proinflammatory state with elevated levels of fibrinogen and with increased concentrations of C-reactive protein, all of which increase the risk of cardiovascular and cerebrovascular events [1, 2]. But in contrast to the overwhelming evidence for the detrimental impact of obesity on the circulatory system, unexpected findings remain showing that overweight or obese patients may have a survival benefit when an acute cardiovascular or cerebrovascular event occurs. The term "obesity paradox" was introduced by Lavie et al. [3] to describe the observation that a high percentage of body fat and high BMI are strong predictors of event-free survival in patients with heart failure. The observations of paradoxically more favorable clinical prognosis in obese than in normal-weight patients with heart failure was also named "reverse epidemiology" [4].

The studies encompassing now many thousands of patients with heart failure have shown evidence that being overweight is associated with decreased mortality as compared not only to underweight, but also with normal-weight patients [5–14]. In a prospective evaluation of all-cause mortality in patients with pre-existing cardiovascular diseases and type-2 diabetes mellitus, the lowest mortality rate was found in obese patients, with BMI 30–35 kg/m^2, i.e. lower than in underweight patients, with BMI < 22 kg/m^2 (hazard ratio – HR 2.96, p = 0.012) and lower than in patients with BMI in the normal range of 22–25 kg/m^2 (HR 1.88, p = 0.019) [6]. In a study of 4417 patients

with cardiovascular disease surveyed over an average of 7.3 years of follow-up, there was a lower risk of all-cause mortality in both overweight (HR 0.73, confidence interval – CI 0.64–0.82) and obese patients (HR 0.84, CI 0.73–0.97), despite more co-morbidities and lower self-related health score [7]. In a group of 1003 patients, aged 66.4 ± 7.8 years, with hypertension and/or type-2 diabetes (pre-clinical heart failure), obesity was associated with a lower risk of death (HR 0.27, CI 0.09–0.85) and reduced risk of hospitalization for cardiac causes (HR 0.54, CI 0.28–0.99) as compared with patients with normal BMI [8]. In a group of 344 patients with advanced systolic heart failure, survival without the need of urgent heart transplant during the two years of observation was 77.9% in patients with high waist circumference vs. 64.3% in patients with low waist circumference ($p = 0.025$), and the best outcomes were seen in patients with both high waist circumference and high BMI [9].

The obesity paradox in patients with very advanced heart failure referred for heart transplant has been confirmed in further studies [10]. In a study of patients with coronary artery disease coexisting with hypertension, there was a lower risk of death and major cardiovascular events in overweight and obese patients as compared to those of normal weight [11]. A review of studies of patients with coronary artery disease has shown that in overweight and mildly obese patients, there was lower cardiovascular mortality and lower total mortality as compared to normal weight patients [12]. The obesity paradox has also been found in elderly patients undergoing coronary artery bypass grafting by sternotomy [13]. The follow-up (for 1037 ± 703 days) of 1205 patients who underwent primary percutaneous coronary intervention confirmed the obesity paradox in a Japanese population, showing that obese patients, with a body mass index (BMI) ≥ 30 kg/m^2, had significantly lower frequency of major adverse cardiac events, all-cause death, cardiac death, and hospital admission for heart failure than patients with BMI < 20 kg/m^2 [14].

Much less is known about the possible existence of the obesity paradox in patients with cerebrovascular diseases. Data on 34,132 Korean patients with acute ischemic stroke has shown that obese patients had a decreased risk of mortality (HR 0.77; CI 0.63–0.93 for BMI 30–32.5 kg/m^2) as compared to the reference level of BMI 20–23 kg/m^2. The obesity paradox in stroke survivors became evident after 90 days after stroke onset and was the most prominent in patients who were less than 65 years old [15]. In a large investigation of 2785 patients with first-ever stroke, obese and overweight subjects had significantly better early and long-term survival rates compared to those with normal BMI [16]. In this study, neurological severity, as estimated by the National Institutes of Health Stroke Scale score, was not different on admission among the obese, overweight and normal-weight patients. Early, i.e. first week, survival was 96.4% in obese patients, 92.8% in overweight patients, and 90.2% in normal-weight patients. The beneficial long-term effects of obesity were found, as 10-year survival, to be 52.5% in obese patients, 47.4% in overweight patients, and 41.5% in normal weight patients ($p < 0.0001$) [16]. In an Asian-Pacific cohort of 1,592 consecutive patients with ischemic stroke, there was a strong ($p = 0.002$) and inverse association of initial neurological severity with obesity and there was an inverse relationship between BMI and long-term mortality (HR for overweight patients 0.77 and for obese patients 0.6) during the median follow-up period of 4 years [12]. The authors of a study of 510 patients who survived a first-ever acute ischemic stroke, using the modified Rankin Scale for measuring the degree of disability or dependence in daily activities, found that BMI < 35 kg/m^2 was associated with increased functional recovery after stroke [17]. In a multi-center trial involving 20,246 subjects (24% of them obese) with recent ischemic stroke, being overweight or obese did not increase the risk of recurrent stroke as compared to lean patients: after adjusting for confounders, the HR for overweight patients was 0.95 (CI 0.85–1.06) and for obese patients was 0.95 (CI 0.83–1.08) [18]. Data from the stroke registry in Denmark 2000–2010, encompassing 38,506 patients with known BMI, has proven the obesity paradox in relation to the recurrence of stroke: there was significantly lower risk of stroke being recurrent in obese (odds ratio 0.9, CI 0.82–0.98) or overweight patients (odds ratio 0.89, CI 0.83–.096) as compared to normal weight patients [19]. In a Korean trail involving 1604 survivors of intracerebral hemorrhage, there was a lower risk of long-term death in overweight patients (HR 0.69; CI 0.49–0.96) and obese patients (HR 0.61; CI 0.43–0.88) [20].

Hypotheses Related to the Obesity Paradox

One of the theories that tries to explain the phenomenon of the obesity paradox emphasizes that adipose tissue provides safe storage of the harmful lipophilic chemicals known as persistent organic pollutants, thus preventing the storage of these toxic materials in other critical organs [21]. Others suggest the importance of taking into consideration the influence of cardiorespiratory

fitness on the results of the studies of the relationship between BMI and survival [22].

A promising hypothesis trying to elucidate the obesity paradox is related to the phenomenon of preconditioning. The idea of preconditioning, i.e. the development of cardioprotective effects as a consequence of short periods of ischemia, was introduced into the medical literature more than 25 years ago [23]. Repeated sublethal ischemia may confer protection from infarction and arrhythmia 24–72 h after the preconditioning stimuli [24]. Subsequently, ischemic preconditioning has been recognized in the central nervous system, developing as an adaptive mechanism after repeated brief episodes of ischemia and protecting the brain against long-lasting ischemia [25–27].

Ozeke et al. [28] postulated that the better outcome for cardiovascular and total mortality in obese and overweight as compared with normal-weight and underweight patients might be related to occult and undiagnosed obstructive sleep apneas. The occurrence of obstructive sleep apneas is strongly related to obesity. Although associated with obstructive sleep apneas, transient periods of oxygen desaturation followed by re-oxygenation, i.e. chronic intermittent hypoxia, exert many harmful systemic effects, mainly through oxidative stress, inflammation, and endothelial dysfunction [29, 30], along with these disadvantageous effects the phenomenon of preconditioning may develop. It has been proposed that obstructive sleep apneas may activate preconditioning-like adaptive mechanisms, protecting the heart and the brain [31–33] against the consequences of ischemia. Thus, the preconditioning-like mechanisms developing as a result of chronic intermittent hypoxia caused by obstructive sleep apneas in obese patients may be one of the underlying mechanisms in explaining the obesity paradox [28].

Doubts About the Obesity Paradox

The problem of the correlation between obesity and better survival of patients with cardiovascular and cerebrovascular disease still remains widely unexplored and it remains questionable whether the obesity paradox truly exists or is a false hypothesis, based on methodological influences [24]. The estimation of obesity based on BMI may be questionable, although this anthropometric measure is the one most commonly used. The other ways of the simple measurement of excessive fat, and especially its abdominal accumulation, are waist circumference, waist-to-hip ratio, and waist-to--height ratio; it is probable that these measurements would make it possible to predict cardiovascular risk better than BMI does [34].

In one of the studies, the mortality rate in patients with atherosclerotic arterial disease in the course of type 2 diabetes decreased significantly with increasing BMI, but when obesity was measured by waist circumference the same rates were stable across waist categories [35].

Akin et al. [36] have studied patients with coronary heart diseases and found no evidence of the obesity paradox. The study encompassed patients who were stratified in three different categories of body weight, i.e. there were 1436 normal weight, 2839 overweight, and 1531 obese patients. These unselected patients underwent percutaneous coronary intervention with drug-eluting, i.e. sirolimus-eluting or paclitaxel-eluting, stents. The authors compared clinical in-hospital and 1-year outcomes in the groups of patients in relation to their body weight. Primary endpoints were the rate of major adverse cardiac and cerebrovascular events (defined as death, myocardial infarction, and stroke), and target vessel revascularization. In normal weight compared to overweight or obese patients, one-year follow-up revealed similar rates of all-cause death (3.3% vs. 2.4% vs. 2.4%, $p = 0.17$), similar rates of major adverse cardiac and cerebrovascular events (7.1% vs. 5.6% vs. 5.5%, $p = 0.09$), and similar rates of target vessel revascularization (10.9% vs. 11.7% vs. 11.6%, $p = 0.56$); thus there was no evidence of the obesity paradox [36]. However, one could point out that the baseline clinical parameters were more severe in overweight and obese patients and, despite that, the delayed outcomes were similar to those in the patients with normal weight.

Zamora et al. [37] studied the obesity paradox in a long-term observation in a group of 297 patients with ischemic heart failure and in a group of 207 patients with non-ischemic heart failure. Most of the patients in each whole group were in NYHA functional class II (51%) or III (42%) and the median left ventricular ejection fraction was as low as 30%. The BMI and survival were assessed after a follow-up of 6.1 years. In the ischemic heart failure patients, hazard ratios of mortality for low weight (BMI < 20.5 kg/m^2), overweight (BMI 25.5 to < 30 kg/m^2), and obese (BMI ≥ 30 kg/m^2) patients were not significantly different as compared with normal weight (BMI 20.5 to < 25.5 kg/m^2) patients. But in contrast to this observation, the data concerning the patients with non-ischemic heart failure showed different mortality rates in the subgroups of patients with different BMI; as compared to normal weight patients, the underweight patients had increased mortality: HR was 2.08 (1.16–3.75, $p = 0.014$) and obese patients had decreased mortality: HR was 0.49

(0.28–0.86, p = 0.01). The results of the study indicated that the obesity paradox was absent in patients with heart failure of ischemic etiology; however, it was observable in the group of patients with non-ischemic heart failure [37].

A study of 37,573 patients followed up for 11 years indicated that in atherosclerotic heart diseases, improved survival related rather to overweight than obese patients, thus promoting an overweight paradox, not obesity paradox [38]. In recently published results of a prospective study on the association between mortality and BMI/waist circumference in the course of acute coronary syndrome in the Arabian Gulf, no protective effect of obesity was found [39].

In a group of 22,216 patients with acute cerebrovascular events, overweight was associated with favorable functional recovery; however severe obesity (BMI $\geq$ 32.5 kg/m^2) was associated with higher 3-month mortality (OR 2.01; 95% CI 1.10–3.69) [40].

Debates pro- and contra the obesity paradox in cardiovascular and cerebrovascular disease continue.

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